AP/1644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	McIntosh, et al.
Serial No.:	09/807,810
Filed:	July 10, 2001
For:	Uses of Fibroblasts or Supernatants from Fibroblasts for the Suppression of Immune Responses in Transplantation
Group:	1644
Examiner:	Ewoldt

Commissioner for Patents
Box 1450
Alexandria, VA 22314-1450

BRIEF BEFORE THE BOARD OF APPEALS AND INTERFERENCES

SIR:

This is an appeal from the Final Rejection dated September 10, 2004.

REAL PARTY IN INTEREST

The real party in interest is Osiris Therapeutics, Inc., the assignee of the claimed subject matter of the above-identified application.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the above-identified application.

STATUS OF CLAIMS

Claims 1, 2, 4-13, 16, 17, 19-22, 24, 26-28, and 30-32 are pending, stand finally rejected, and are before the Board on appeal. These claims are listed in the Appendix attached hereto.

Claims 3, 14, 15, 18, 23, 25, 29, and 33 have been withdrawn from consideration.

STATUS OF AMENDMENTS

No amendments after the Final Rejection have been filed.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention, in one aspect, as defined in Claim 1, is directed to a method of inducing a reduced immune response to donor tissue in a transplant recipient. The method comprises treating the recipient with at least one member selected from the group consisting of isolated fibroblasts and a supernatant from an isolated fibroblast culture in an amount effective to reduce an immune response in the recipient to the transplanted donor tissue. Support in the specification is found in the fourth and fifth paragraphs of Pages 2, the fifth paragraph of Page 4, the paragraph bridging Pages 5 and 6, and in the paragraph bridging Pages 9 and 10.

In another aspect of the present invention, there is provided, as defined in Claim 16, a method of reducing an immune response against recipient tissue by donor tissue. The method comprises contacting the donor tissue with at least one member selected from the group consisting of isolated fibroblasts and a supernatant from an isolated fibroblast culture in an amount effective to reduce an immune response by the donor tissue against the recipient. Support is found

in the specification in the fifth paragraph of Page 3, the fourth and fifth paragraphs of Page 4, from the paragraph bridging Pages 6 and 7 to the second paragraph of Page 8, and in the paragraph bridging Pages 9 and 10.

In yet another aspect of the present invention, there is provided, as defined in Claim 27, a method of treating a transplant recipient for graft versus host disease. The method comprises treating the recipient of a transplant with at least one member selected from the group consisting of isolated fibroblasts and a supernatant from an isolated fibroblast culture in an amount effective to reduce an immune response against the recipient by the transplanted donor tissue. Support is found in the specification in the fifth paragraph of Page 3, the fourth and fifth paragraphs of Page 4, from the paragraph bridging Pages 6 and 7 to the second paragraph of Page 8, and in the paragraph bridging Pages 9 and 10.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed by the Board on appeal:

(i) the rejection of Claims 1, 2, 4, 5, 8, 9, 11-13, 16, 17, 19, 21, 24, 26-28, 30, and 32 under 35 U.S.C. 102(b) as being anticipated clearly by Soiffer, et al. as evidenced by U.S. Patent No. 5,736,396; and

(ii) the rejection of Claims 6, 7, 10, 20, 22, and 31 under 35 U.S.C. 103 as being unpatentable over Soiffer, et al. in view of Donnelly, et al.

ARGUMENT

Soiffer discloses bone marrow transplantation employing CD6 depleted allogeneic bone marrow for acute leukemia in patents in first remission. Such

treatment was found to be effective in consolidating remissions of high-risk patients with acute leukemia in first remission without excessive toxicity.

The Examiner has taken the position that because the '396 patent teaches that bone marrow includes fibroblasts, Soiffer, which teaches bone marrow transplantation, anticipates the claimed invention. Soiffer, however, does not disclose or even remotely suggest to one of ordinary skill in the art a method of inducing a reduced immune response to donor tissue, or a method of reducing an immune response against recipient tissue by donor tissue, of a method of treating a transplant recipient for graft versus host disease by administering isolated fibroblasts or a supernatant from an isolated fibroblast culture.

At Page 3, lines 3-5 of the Final Rejection, the Examiner states that, "'Isolated,' however, can be defined as separated or detached, thus, the fibroblasts need not be purified but only separated form their original source, i.e., the donor's bone."

It is clear that from reading the specification, that when Applicants refer to isolated fibroblasts, they do not mean fibroblasts that merely are removed from the donor's bone or any other tissue where fibroblasts may be present. For example, at Page 7, lines 22-27, the specification states that the fibroblasts can be administered with bone marrow cells or hematopoietic stem cells, which are another group of cells, different from fibroblasts, which have been separated from bone.

> Thus, in the context of bone marrow (hematopoietic stem cell) transplantation, attack of the host by the graft can be reduced or eliminated. Donor marrow can be pretreated with isolated fibroblasts prior to implant of the bone marrow or peripheral blood stem cells into the recipient. The fibroblasts inhibit or reduce the T-cell response such as to reduce or eliminate a recipient from being adversely affected by the donor tissue, i.e., the therapy reduces or eliminates graft versus host response.

(Specification, Page 7, lines 22-27).

Thus, it is clear that Applicants do not intend merely to remove the fibroblasts from bone in that the fibroblasts, which can be one component of bone marrow (or from a source other than bone marrow), are used to treat another component of bone marrow, i.e., hematopoietic stem cells, in order to reduce or eliminate a graft versus host response.

In addition, contrary to the Examiner's assumptions and assertions, the fibroblasts need not be isolated solely from bone marrow. For example, the fibroblasts may be obtained from skin, as indicated at Page 9, lines 24 and 25:

> Although the invention is not limited thereof, fibroblasts can be obtained from skin for use in the methods described herein.

Also, as shown in Example 1, at Page 11, lines 20-22 as follows, the specification provides a working example in which the fibroblasts were obtained from skin:

> Fibroblasts were human normal skin fibroblasts CCD-1087 Sk from 18 years old female obtained from ATCC (Cat # CRL-2104) and were maintained in DMEM – low glucose/10% FCS.

In addition, the present invention also is directed to the use of supernatants derived from fibroblast cultures. Such a supernatant is employed in Example 3.

Therefore, it is clear form the specification of the above-identified application that when Applicants refer to "isolated" fibroblasts, Applicants do more than just separate the fibroblasts form bone or other tissue.

For example, assuming that Applicants can obtain the fibroblasts from bone, it is clear that from reading the specification that the fibroblasts would be separated from other cells in the bone marrow, such as hematopoietic stem cells, before they are employed in the methods of the present invention. For example, it is clear from Page 7, lines 22-27 that the isolated fibroblasts are administered to another isolated group of cells from bone marrow, i.e., hematopoietic stem cells, in order to prevent or reduce or eliminate a graft versus host response.

In addition, the present invention also is directed to the use of supernatants from fibroblast cultures. One skilled in the art would understand that, in order to obtain such supernatants, one would need to isolate the fibroblasts from other cells, and then culture the isolated fibroblasts in order to obtain the supernatants.

Applicants, in isolating the fibroblasts, clearly undertake steps in addition to the mere removal of a mixture of cells including fibroblasts from bone or other tissue. Thus, when read in the context of the specification, the term "isolated" does not read upon the mere separation of the fibroblasts from bone, as the Examiner asserts.

For the above reasons and others, Soiffer does not anticipate Applicants' claimed invention, nor does Soiffer render Applicants' claimed invention obvous to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reversed.

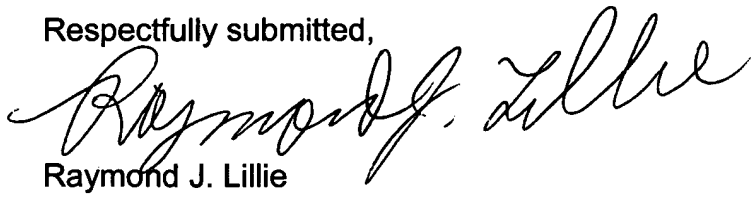
With respect to the rejection under 35 U.S.C. 103, Soiffer does not disclose or even remotely suggest to one of ordinary skill in the art the administration of isolated fibroblasts or a supernatant from an isolated fibroblast culture in order to induce a reduced immune response to donor tissue, to reduce an immune response against recipient tissue by donor tissue, or to treat a transplant recipient for graft versus host disease.

Donnelly teaches that corneal stromal fibroblasts did not induce proliferative responses by allogeneic peripheral blood mononuclear cells *in vitro*, and that such fibroblasts inhibited mixed leukocyte reactions between peripheral blood mononuclear cells of allogeneic donors. Donnelly, however, does not disclose or even remotely suggest to one of ordinary skill in the art that one may administer isolated fibroblasts or a supernatant from an isolated fibroblast culture in order to induce a reduced immune response against donor tissue, to reduce an immune response against recipient tissue by donor tissue, or to treat a transplant recipient for graft versus host disease.

The combination of Soiffer and Donnelly, therefore, does not even remotely suggest to one of ordinary skill in the art that one may administer isolated fibroblasts or a supernatant from an isolated fibroblast culture, in order to induce a reduced immune response against donor tissue, to reduce an immune response against recipient tissue by donor tissue, or to treat a transplant recipient for graft versus host disease. Because the combination of Soiffer and Donnelly does not even remotely suggest Applicants' claimed methods to one of ordinary skill in the art, the combination of Soiffer and Donnelly fails to meet the standard for obviousness set by 35 U.S.C. 103. It is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reversed.

For the above reasons and others, it is respectfully requested that the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103 be reversed.

Respectfully submitted,



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APPENDIX - CLAIMS ON APPEAL

1. A method of inducing a reduced immune response to donor tissue in a transplant recipient, comprising treating the recipient with at least one member selected from the group consisting of isolated fibroblasts and a supernatant from an isolated fibroblast culture in an amount effective to reduce an immune response in the recipient to the transplanted donor tissue.

2. The method of claim 1 wherein said at least one member is isolated fibroblasts.

4. The method of claim 2 wherein the fibroblasts are allogeneic to the recipient.

5. The method of claim 4, wherein the fibroblasts are obtained from the donor of the transplant.

6. The method of claim 2 wherein the fibroblasts are allogeneic to both the donor of the transplant and the recipient.

7. The method of claim 2, wherein the fibroblasts are administered to the recipient prior to administration of the transplant.

8. The method of claim 2, wherein the fibroblasts are administered concurrently with administration of the transplant.

9. The method of claim 8, wherein the fibroblasts are administered as a part of the transplant.

10. The method of claim 2 wherein the fibroblasts are administered after transplant.

11. The method of claim 2 wherein the fibroblasts are administered to the transplant recipient to treat rejection of the transplant by the recipient.

12. The method of claim 2, wherein the fibroblasts are human.

13. The method of claim 1, further comprising administering to the recipient immunosuppressive agents.

16. A method of reducing an immune response against recipient tissue by donor tissue, comprising contacting the donor tissue with at least one member selected from the group consisting of isolated fibroblasts and a supernatant from an isolated fibroblast culture in an amount effective to reduce an immune response by the donor tissue against the recipient.

17. The method of claim 16 wherein said at least one member is isolated fibroblasts.

19. The method of claim 17, wherein the fibroblasts are autologous to the donor.

20. The method of claim 17, wherein the fibroblasts are allogeneic both to the donor and to the recipient of the donor tissue.

21. The method of claim 17, wherein the donor tissue and the fibroblasts are contacted *ex vivo* prior to transplantation of the donor tissue.

22. The method of claim 21, wherein the donor tissue is exposed to recipient tissue prior to being contacted with the fibroblasts.

24. The method of claim 16 wherein the donor tissue is bone marrow.

26. The method of claim 16, further comprising administering to the recipient immunosuppressive agents.

27. A method of treating a transplant recipient for graft versus host disease, comprising treating the recipient of a transplant with at least one member selected from the group consisting of isolated fibroblasts and a supernatant from an isolated fibroblast culture in an amount effective to reduce an immune response against the recipient by the transplanted donor tissue.

28. The method of claim 27 wherein said at least one member is isolated fibroblasts.

30. The method of claim 28, wherein the fibroblasts are autologous to the donor.

31. The method of claim 28, wherein the fibroblasts are allogeneic to both the donor and recipient.

32. The method of claim 27, further comprising administering to the recipient immunosuppressive agents.

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